REMARKS

Claims 1-34 are pending in the application. Claims 6, 7, and 22-28 are withdrawn as being drawn to non-elected inventions. New claims 31-34 are added. Claims 1-5, 8-21, 29 and 30 are under active consideration.

Claim 1 has been amended to recite that the first replication-defective gene delivery vehicle is administered mucosally according to a multiple dose schedule. Support for the amendment can be found in the specification, for example, at page 35, lines 19-20; and page 40, lines 4-5. Accordingly, the specification provides adequate support for the amendment. Claim 1 has been amended to further clarify the intended subject matter of the claimed invention. No new matter has been added with the claim amendment.

Support for new claims 31-34 can be found in the specification, for example, at page 35, lines 21-28. Entry of the new claims is therefore respectfully requested.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Rejection under 35 U.S.C. § 102(e)

Claims 1-5, 8-14, 16-20, 29, and 30 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by the reference of Malone et al. (U.S. Patent No. 6,110,898). In particular, the Office Action alleges that "Malone anticipates Applicants' invention because it discloses a method of inducing a mucosal immune response wherein an antigenic polynucleotide is administered to the vaginal, nasal or rectal mucosal membranes of a subject (Abstract, lines 2-4; col. 14, lines 64-66; col. 15, lines 57-62; and col. 17, lines 61-63)" and that "Malone further provides that the polynucleotide is delivered by an alphaviral vector such as Sinbis or Semliki Forest virus (col. 11, lines 39-41)" and "Malone's alphaviral vector comprises a replicon (col. 2, lines 66-col. 3, line 1)" (Final Office Action, page 3). In addition, the Final Office Action alleges that "Malone inherently discloses presenting an antigenic polynucleotide to dendritic cells" and that "Malone also teaches eliciting an HLA class I or HLA class II response through inherency" (Final Office Action, page 3). Applicants respectfully traverse the rejection under 35 U.S.C. § 102(e) on the following grounds.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102, "the reference must teach every aspect of the claimed invention either explicitly or implicitly." M.P.E.P. § 706.02. Applicants respectfully submit that the reference of Malone et al. does not teach all aspects of the Applicants' invention, either explicitly or implicitly.

As amended, claim 1 recites a method of generating an immune response in a subject, comprising mucosally administering to target cells a first replication-defective gene delivery vehicle comprising a polynucleotide encoding at least one first antigen or modified form thereof, wherein the first replication-defective gene delivery vehicle is administered mucosally according to a multiple dose schedule. Applicants' specification defines a multiple dose schedule as "one in which a primary course of vaccination may be with 1-10 separate doses, followed by other doses given at subsequent time intervals" (page 35, lines 20-22). For example, in methods of immunization employing multiple steps (*e.g.*, prime-boost administration), multiple doses may be administered at one or more steps.

In contrast, the reference of Malone et al. teaches a single dose administration (see col. 16, lines 47-51). Moreover, Malone et al. fail to teach any specific dosing schedule. Rather, Malone et al. merely state that "it is sufficient that the gene expression vectors be supplied at a dosage sufficient to cause expression of the antigenic polypeptide encoded by the polynucleotide sufficient to induce the desired protective immunity as characterized by production of sIgA, for instance as confirmed by lung lavage" (col. 16, lines 52-57). Such a statement may be regarded as no more than an invitation to experiment. The sole example of a mucosal immunization regimen, disclosed by Malone et al., utilizes a single intranasal administration of alphavirus particles to mice (see Example 1 at col. 17, lines 61-64).

Furthermore, Malone et al. teach away from the claimed methods of the instant application. Malone et al. emphasize that the antigen-encoding polynucleotide must be administered at a mucosal inductor site adjacent to or containing local aggregates of mucosal associated lymphoid tissue (col. 5, line 65 through col. 6, line 1). See col. 19, lines 43-55 as follows:

> We conclude from these observations that the development of effective genetic or recombinant viral vaccines will be greatly facilitated by incorporating treatment modalities or targeting functionality which will result in antigen expression either within mucosal inductor tissues or epithelial cells overlying such tissues, where antigens can be sampled, processed and delivered by dendritic cells to responsive T and B cells. Administration of gene expression vectors to nonspecific mucosal effector tissues may

result in responses which include anergy and/or local but not generalized mucosal immunity, and that such non-targeted patterns of mucosal transduction or transfection may result in systemic but not mucosal immunity.

In contrast, the instant application provides evidence that the claimed methods of mucosal administration according to a multiple dose schedule are effective in stimulating mucosal immune responses, and induce both humoral and cellular immunity. See specification, for example, at Examples 1-8 at pages 39-52.

Malone et al. fail to teach the claimed methods of mucosal administration. Therefore, Malone et al. fail to teach all the limitations of the claims, and withdrawal of the rejection under 35 U.S.C. § 102(e) is respectfully requested.

Rejections under 35 U.S.C. § 103

A. Claim 15 in view of Malone et al. and Parker et al.

Claim 15 is rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Malone et al. (U.S. Patent No. 6,110,898) in view of the reference of Parker et al. (U.S. Patent No. 6,261,570). In particular, the Final Office Action alleges that "Parker discloses vaccines directed against numerous alphavirus pathogens" and "also discloses expressing antigens of other alphaviruses as chimeric alphaviruses for use as potential vaccines for humans (col. 5, lies 39-51)." The Final Office Action further alleges that "it would have been obvious to one of ordinary skill in the art to modify Malone to include the teachings of Parker as this combination would provide a method for inducing mucosal immunity against a variety of alphaviral pathogens" (Final Office Action, page 4). Applicants respectfully traverse the rejection.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure." M.P.E.P. § 706.02.

Applicants submit that the cited references do not disclose or suggest all the limitations of the present invention. Thus, a *prima facie* case of obviousness has not been presented by the Office, and the cited combination is based on impermissible hindsight reconstruction.

As acknowledged by the Examiner, the reference of Malone et al. does not teach or suggest the use of a chimeric alphaviral vector comprising elements from two or more alphaviruses. For the reasons noted above, Malone does not teach or suggest methods of immunization by administration of a replication-defective gene delivery vehicle mucosally according to a multiple dose schedule, as claimed. The secondary reference of Parker et al. fails to cure the deficiencies of Malone et al. Parker et al. describes vaccination against alphaviruses using live attenuated alphaviruses, which may include chimeric alphaviruses. The use of chimeric alphaviruses is described for the purpose of improving immunogenicity against a range of alphavirus subtypes. Furthermore, the chimeric virus is described as attenuated, but not replication defective. The reference of Parker et al. fails to teach or suggest the use of a replication defective alphaviral vector encoding a non-alphaviral antigen. Parker et al. also fails to provide any incentive for inserting polynucleotides encoding non-alphaviral antigens for vaccination against pathogens other than alphavirus as taught in the instant application.

Thus, there is no combination of Malone with Parker that can render pending claim 15 obvious and withdrawal of this rejection is in order.

B. Claim 21 in view of Malone et al. and De Plaen et al.

In addition, claim 21 is rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Malone et al. (U.S. Patent No. 6,110,898) in view of the reference of De Plaen et al. (U.S. Patent No. 5,612,201). In particular, the Office Action alleges that "De Plaen teaches administering a MHC sequence to a target cell prior to transformation of the target cell" and that "it would have been obvious to one of ordinary skill in the art, to modify Malone to include the teachings of De Plaen since this combination would improve the immunogenicity of Malone's method of mucosal immunization" (Final Office Action, page 5).

As acknowledged by the Examiner, the reference of Malone et al. does not teach or suggest the use of a MHC-I or MHC-II sequence for enhancing mucosal immunity. The secondary reference of De Plaen et al. teaches methods of generating an immune response against tumor rejection antigens. In particular, De Plaen et al. describe transfecting cells with an MHC/HLA coding sequence to promote presentation of tumor rejection antigens at the cell surface. However, neither the reference of De Plaen et al. nor the reference of Malone et al.

teach or suggest the claimed method of mucosally administering to target cells a polynucleotide encoding at least one antigen according to a multiple dose schedule.

Therefore, the references of Malone et al. and De Plaen et al. either singly or in combination fail to teach or suggest all the limitations of the claims, and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Request for Interview

Applicants request an interview with the Examiner prior to issuance of the next Office Action.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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